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ABSTRACT

This proposal is focused on the three-dimensional NIR imaging reconstruction using ultrasound localization for cancer detection and diagnosis. During the reported period, we have achieved simultaneous reconstruction of optical absorption and scattering coefficients of heterogeneities using a dual-mesh scheme based on finite element method, and introduced a new simple two-layer model to correct diffusive wave distortion caused by underlying chest wall of patients.

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INTRODUCTION

Breast cancer ranks second among cancer deaths of women in United States. Functional imaging with near infrared (NIR) diffused light has found potential applications in breast cancer detection and characterization [1-3]. The most important functional parameters it provides are the hemoglobin concentration and oxygen saturation, which are deduced from wavelength-dependent lesion absorption measurements. However, due to the intense light scattering, diffused light probes a widespread region instead of providing information along a straight line. Multiple measurements are always correlated as a result of overlapping of probed regions. Therefore, increasing the total number of measurements does not necessarily provide more independent information for image reconstruction. In general, the inverse image reconstruction is underdetermined and ill-posed. Reconstruction with the aid of *a priori* target geometry information provided by co-registered ultrasound has shown promising results in improving the accuracy of reconstructed optical properties and the localization of targets [4-7].

The main objective of this research is focused on the study of three-dimensional NIR imaging reconstruction using ultrasound localization for breast cancer detection and diagnosis.
From more than 100 breast patients studied so far, we have obtained promising results [4-9], but also encountered problems, which are listed below. We have studied each problem extensively and have found solutions or partial solutions to solve the problems.

1). In optical imaging with diffusive light, a common problem is the inter-parameter crosstalk between absorption and scattering coefficients. For example, a localized absorption heterogeneity turns into a scattering heterogeneity in the reconstructed images, or vice versa. It is well known that optical absorption in breast tissue is primarily related to hemoglobin concentration and oxygen saturation, and breast cancers are presumed to have higher blood volume than healthy benign lesions. Therefore, separation of absorption and scattering perturbations is very important for cancer diagnosis. Several groups have conducted research along this line, and some promising results have been obtained using transmission geometries [10-12]. In the transmission geometry, the breasts were either inserted in a liquid filled tank with optical sources and detectors deployed around the breasts or breasts were sandwiched between two parallel plates with sources deployed on one plate and detectors on the opposite plate. We proposed simultaneous reconstruction of absorption and scattering heterogeneities based on light reflection geometry where patients were scanned in supine positions as ultrasound scans. A column normalization method to the weight matrix obtained from FEM forward model is introduced to correct the depth dependent problem and to alleviate the crosstalk between the absorption and scattering coefficients [9,13]. With this approach, phantom targets with both absorption and scattering heterogeneities can be reconstructed with good contrast and resolution. With this approach, the contrast between malignant breast cancers and benign lesions can be further improved compared with that obtained from the dual mesh scheme based on Born approximation, where the bulk reduced scattering coefficient has been used for reconstructing absorption heterogeneities .

2). The chest-wall layer underneath the breast tissue consists of muscles and bones and induces distortion to near infrared diffused wave measured at distant source-detector pairs when the patient is imaged in the supine position. Since conventional ultrasound is used in pulse-echo reflection geometry, it is desirable to acquire optical measurements with the same geometry. Compared with transmission geometries, the reflection geometry has the advantage of probing reduced breast tissue thickness because patients are scanned in the supine position. Consequently, lesions closer to the chest wall can be imaged. In general, the breast tissue thickness has been reduced to less than 3 to 4 cm. However, when the chest wall is present within 1.5 to 2 cm from the skin surface, the semi-infinite geometry is not a valid assumption for optical measurements and the chest wall underlying the breast tissue affects the optical measurements obtained from distant source-detector pairs. In general, the symmetric location of the contralateral normal breast is chosen as the reference site to minimize the effect of the chest wall. Fig. 1(a) illustrates the problem when multiple source and detector fibers are deployed on the breast for co-registered imaging. The light reflectance measurements at distant detector positions from the sources consist of mixed signals from both breast tissue and chest wall and are distorted. Fig. 1 (b) is the ultrasound image of the breast where the tilted chest wall marked by white arrows can be seen. Fig. 1(c) plots the light reflectance (log scale) measured at the surface of the probe versus source-detector separation ρ. If the semi-infinite assumption were valid, the plot of reflectance (log scale) vs. ρ should be linear. However, when the light penetrated deeper and hence received by detectors at larger distances from the sources, the deviation from the linearity was clearly seen in the plot.

The distorted distant measurements can be quite complex. In some patients, the measured distant amplitude profiles consist of many random points, while in others, the amplitude profiles bend considerably from expected linear curves. In general, when the amplitude values are low, the phase profiles behave like random variables. As a result, measurements beyond a certain distance must be removed before imaging. Since the depth of chest wall and average breast tissue absorption and scattering coefficients vary from patient to patient, it is difficult to predict the cutoff source-detector distance. As a consequence, the data processing and image reconstruction must be done off-line for each individual patient by examining the data and removing distant measurements.

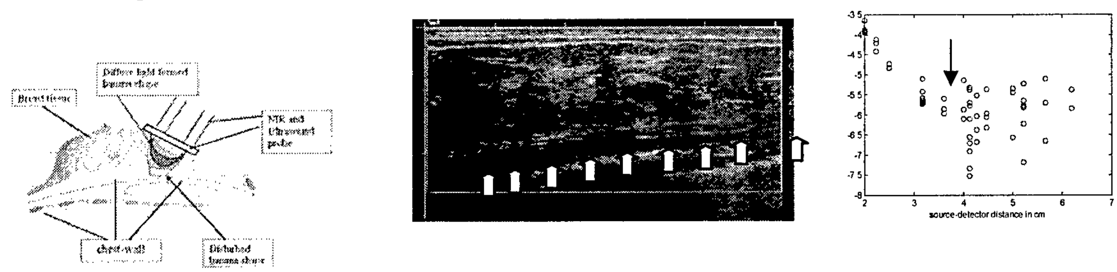

Fig.1. (a) Illustration of the chest-wall induced distortion. (b) Ultrasound image of a small cyst (red arrow) with titled chest wall marked with an array of white arrows and (c) the light reflectance R(ρ) (log (ρ^2R(ρ) vs. ρ) measured at the surface of the breast. ρ is the source detector separation. The curve was linear up to about 4 cm of source-detector separation marked by the black arrow.

Although the simple filtering approach introduced by our group can largely eliminate the distorted distant measurements [14], there are clinical cases in which the measured amplitude and phase profiles bend from the expected linear curves due to the influence of the chest-wall layer. It is difficult to cut the curved measurements without losing information content in the process. A simple correction method based on the two-layer model was introduced to fit the measured amplitude and phase profiles after filtering out distant source-detector measurements and to estimate the second-layer optical properties, which can be incorporated into the imaging reconstruction. Since numerical reconstruction algorithms based on FEM are suitable for complex boundary conditions, we have adopted the FEM commercial package FEMLAB for the correction scheme discussed below. The details can be found in Ref 15 and summaries are given in BADY section.

In the next step, we will focus on processing more patient data to give a conclusive report on cancer characterization. Due to the extremely high computation cost (one week to process one patient's data), we have computed a small number of examples reported in the papers. The limited cases are certainly far too early for any conclusion. It is also unwise to use this slow version to compute hundreds of cases.

The costly computation is mainly related to the weight matrix calculation. Since we rely on the commercial FEM solver whose source codes are unavailable to users, we have to perform many steps of calculations to extract intermediate matrixes to form the final weight matrix we need for image reconstruction. If we can generate own FEM codes, the computation time will be significantly reduced. During the reported period, the PI had spent significant amount of time to develop our own FEM codes and more details are given below.

BODY:

1. Simultaneous reconstruction of optical absorption and scattering distributions with ultrasound localization

In optical imaging with diffusive light, a common problem is the inter-parameter crosstalk between absorption and scattering coefficients. In previously reported approach, we have used bulk absorption and reduced scattering coefficients obtained from the fitting results of normal breasts to compute the weight matrices. Then, modified Born approximation was used to reconstruct the absorption variations of both lesion and background.

Since scattering changes also contribute to the measured perturbations, we have attempted to reconstruct both absorption and reduced scattering changes simultaneously, but have not been successful with the modified Born approximation. To solve this problem, a column normalization method has been applied to the weight matrix obtained from FEM forward model to correct the depth dependent problem and to alleviate the crosstalk between the absorption coefficient and scattering coefficient. Different

normalization factors have been assigned to the target region of a finer mesh grid and non-target region of a coarse mesh grid to incorporate the *priori* target information from the co-registered ultrasound images. The dual-mesh scheme minimizes the total number of unknowns and improves under-determined inversion problem.

Details of the reconstruction algorithm and results have been documented in Ref 13 and summarized here. Preliminary results with dual-mesh FEM have indicated that the reconstructed maximum absorption coefficients of benign lesions were 6% to 40 % lower than the corresponding results obtained from the dual-mesh modified Born approximation, while the maximum absorption coefficients of malignant cancers were either higher (8%- 36%) or lower (2%-18%) than the corresponding results obtained from the dual-mesh Born approximation (see Fig. 2). As a result, the absorption and the total hemoglobin contrasts between malignant and benign lesions have been improved. The improvement was due to more accurate background tissue scattering calculation, which could be attributed to the absorption distribution if absorption alone was reconstructed. However, our sample size is too small to draw a conclusion and more cases are being computed. The current limitation is the intensive computation time needed for the forward matrix calculation of dual-mesh FEM, and we are working on implementing the related commercial FEMLAB codes into specialized C codes to speed up the computation.

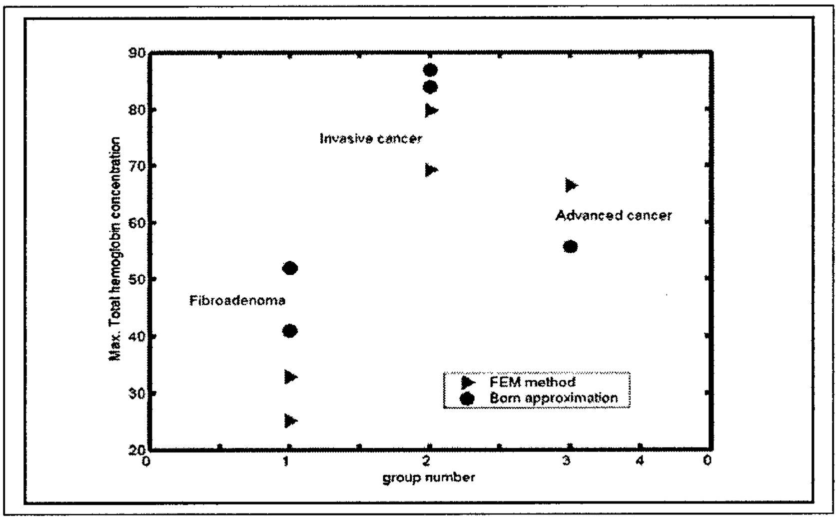

Fig.2. Comparison of reconstructed maximum total hemoglobin concentration obtained from dual-mesh Born approximation (blue, solid circle) and dual-mesh FEM with simultaneous μ_a and μ_s' reconstruction (red solid triangle). Horizontal axis is the patient group number. Two benign lesions (#1, left), two early stage invasive cancers (#2, middle), and one advanced cancer (#3, right). The vertical axis is the reconstructed total hemoglobin concentration.

2. Two-layer model for NIR breast imaging with the assistance of ultrasound

The chest-wall layer underneath the breast tissue consists of muscles and bones and induces distortion to measured near infrared diffused wave when the patient is imaged in the supine position. Since the hand-held probe is made of black plastic, we have adopted

the semi-infinite geometry as the model and have used bulk absorption and reduced scattering coefficients obtained from the fitting results of normal breasts to compute the weight matrices [4-9].

However, for small breasts, the chest wall often appears within 1-2 cm distance from the skin surface. As a result, the NIR measurements at distant source-detector pairs are distorted [14] and the simple semi-infinite geometry model is not accurate. To solve this problem, we have introduced a simplified two-layer model to model the breast tissue and chest wall. A fitting method is adopted to estimate the optical properties of the first layer, normal breast tissue, and the second layer, chest wall. Then, a simple correction scheme is applied to correct the distortion caused by the chest-wall mismatch between the reference site and lesion site. With this method, phantom targets with both absorption and scattering changes from the background can be reconstructed with good contrast and resolution. Initial clinic results have also shown improved contrast between malignant breast cancers and benign lesions, compared with that obtained from the modified Born approximation, where semi-infinite boundary is used [15].

The details of two-layer model with chest wall correction scheme are documented in Ref. [15]. The conclusion is that with this scheme, phantom targets located on top of the chest wall phantom layer can be reconstructed with good contrast and resolution. With the a priori chest wall depth information obtained from ultrasound at both normal and lesion regions, both the reconstructed absorption and resulting total hemoglobin concentration are reduced by about 40%. And the contrast between malignant breast cancers and benign lesions is further improved compared with that obtained from the modified Born approximation, where semi-infinite boundary is used.

3. Generating FEM code using C language for DOT application

PI had identified that the costly computation based on FEM is mainly related to the weight matrix calculation. Since we rely on the commercial FEM solver whose source codes are unavailable to users, we have to do many steps of calculation to extract several intermediate matrixes to form the final weight matrix needed for imaging reconstruction. If we can generate our own FEM codes, the computation time can be significantly reduced.

During the reported period, the PI has studied the theory of FEM calculation, worked on the MATLAB version of FEM code. Since MATLAB is highly inefficient in memory, the MATLAB version can only deal with a limited amount of element numbers, which implies that the FEM mesh cannot be fine enough to reach certain accuracy. The PI has turned the Matlab codes to C language codes to solve the memory problem. So far, the C codes can solve the forward model, but more work has to be done to solve the inverse problem.

KEY RESEARCH ACCOMPLISHMENTS:

- Solved the cross-talk problem between absorption coefficient and scattering coefficients by using a column normalization scheme and dual mesh scheme based on finite element method;
- Introduced a two-layer model to solve the chest wall distortion problem.
- Assisted in the clinic study performed in the Health Center of the University of Connecticut.
- Conducted research to speed up the image reconstruction by translating FEM codes into C codes.

REPORTBALE OUTCOMES:

Presentations and posters:

Huang MM and Zhu Q, "Correction of chest wall induced diffusive wave mismatch with the ultrasound localization. SPIE Proceedings: PW05B-BO117-88

Huang MM and Zhu Q, "Simultaneous reconstruction of absorption and scattering maps," SPIE Proceedings: PW05B-BO117-89 (2005)

Zhu Q, Kurtzman S, Cronin E, Kane M, Huang MM, Xu C, Chen NG, Piao DQ Hegde P, Tannenbaum S, Jagjivan B, Zarfos K , "Tumor angiogenesis and tumor hypoxia as diagnostic indices for differentiation of benign versus malignant breast masses,"SPIE Proceedings: PW05B-BO117-86 (2005)

The PI has given two talks at SPIE Biooptics meeting this January and has learned great deal on biooptics methods, techniques that can be potentially used for breast cancer research. The PI has attended DOD Era of Hope meeting this past June and learned great deal on cancer biology.

Journal papers (Sept 2004 to July 2005):

[1] Huang MM., Zhu Q, "A Dual-mesh optical tomography reconstruction method with depth correction using a priori ultrasound information," Applied Optics, 43(8), 1654-1662, 2004.

[2] Huang MM., Zhu Q., "A correction method of chest-wall induced diffused wave distortion with the assistance of ultrasound," Applied Optics. Accepted under revisions.

[3] Huang MM., Zhu Q., "Initial clinical results of optical absorption and scattering distributions of breast lesions," To be submitted to Technology in Cancer Research & Treatment.

[4] Zhu Q., Cronin E., Currier A., Huang, M.M., Chen NG., Xu, C., "Benign versus Malignant Breast Masses: Optical Differentiation using US to Guide Optical Imaging Reconstruction, Radiology, Oct Issue 2005.

[5] Zhu, Q, Kurtzman, S, Hegde, P., Tannenbaum S, Kane, M, Huang, MM, Chen, NG, Jagjivan B, Zarfos, K, "Utilizing optical tomography with ultrasound localization to image heterogeneous hemoglobin distribution in large breast cancers," Neoplasia, 7(3), 263-270, (2005).

CONCLUSIONS AND FUTURE WORK:
The originally proposed tasks were attached. The PI has successfully completed all the proposed tasks and results have been reported in Refs, 9, 13, 15 and 16. The only remaining task in the original statement of work was to incorporate the 3-D FEM based optical imaging with the 3-D ultrasound imaging that we have developed in the lab. The newly appointed PI, Andres Aquirre, will continue this task.

In addition, the PI has identified the new problem on computation speed using FEM based imaging algorithms. Initial estimation based on the C language codes written by the PI indicates that the imaging speed can be significantly reduced from one week to couple of hours. Therefore, we will be able to process more patients' data, which is critical to establish statistics of the new method. The new PI, Andres Aquirre, has 5 years working experience in software development, including C+, Visual Basics, Matlab, Java and is highly qualified to continue this task.

On-line imaging is still a challenge with the current computing power if we use dual-mesh FEM, which is more flexible and accurate when dealing with complex boundary conditions. However, on-line imaging is particularly valuable for providing timely diagnosis to surgeons and radiologists. Our lab has extensive experience in digital signal processing (DSP) hardware-based instrumentation, such as ultrasound systems [17], and optical coherence tomography (OCT) systems [18]. The DSP-based OCT system we developed in Ref. 18 has the advantage of embedding any desired imaging algorithm and the flexibility of modifying imaging parameters through front panel written in LabVIEW. The new PI is planning to investigate and explore a DSP hardware platform for on-line image reconstruction. The estimated reconstruction time for dual-mesh FEM using a DSP implementation is less than one hour. We estimate the reconstruction time based on being able to take advantage of the parallelism within the reconstruction algorithm. The chosen DSP hardware will support multiple-processors, and the chosen hardware also supports inter-communication among the DSP's either via direct links or shared dual access memory. We must also note that forward weight matrix variables have a wide dynamic range. Thus, the candidate DSP processor will support floating-point arithmetic instead of a fixed-point DSP. A floating-point DSP will also aid in decreasing development time. We also recommend that the chosen DSP have a multi-core/arithmetic logic unit on-board as well as on-chip memory to avoid any latency/wait-states. A multi-core and on-chip memory digital signal processor will enable a more efficient implementation and therefore aid in reaching our estimated reconstruction time.

Originally Proposed tasks.

Task 1: Experimentally evaluate the NIR reconstruction results using reflection geometry without/ with ultrasound localization (months 1~12).

a. Compute a 3D forward model for reflection geometry using finite element method
b. Conduct experiments with targets of different contrasts and sizes located at different depths and spatial locations

c. Evaluate the depth dependent issues.

Experimentally evaluate the NIR reconstruction results using transmission geometry without/with ultrasound guidance (months 12~24).

a. Compute a 3D forward model for transmission geometry using finite element method.
b. Conduct experiments with targets of different contrasts and sizes located at different depths and spatial locations and evaluate the depth dependent issues.

Task 2: Compare 3D reconstruction results obtained from 3D reflection geometry and 3D transmission geometry (months 24~36).

a. Experimental evaluations and comparisons of NIR 3D reconstruction results Optimizing the combined probe design for future clinical experiments.

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